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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

UNGAR, SUSAN NMN

ART UNIT PAPER NUMBER

1642

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/684,599

Applicant(s)

PASTAN ET AL.

Examiner

Susan Ungar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on June 27, 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 19-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 19-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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1. Upon review and reconsideration, the finding of lack of responsiveness mailed August 16, 2002 is hereby withdrawn.
2. The Amendment filed June 27, 2002 in response to the Office Action of December 19, 2001 is acknowledged and has been entered. Previously pending claim 17 has been cancelled and claims 19-32 have been added. Claims 19-32 are currently being examined.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC ' 112

4. Claims 19-32 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides.

The specification teaches that it would be useful to have antibodies that recognize differentiation antigens on solid tumors but that only a small number of these are available (p. 1, lines 34-40) and further teaches that an antibody

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previously isolated reacts with many ovarian cancers and mesotheliomas as well as normal mesothelial cells as well as some cells in the trachea (p. 2, lines 20-25). The antigen recognized by MabK1 appears to be a differentiation antigen present on mesothelium and is expressed on cancers derived from mesothelium as well as on most ovarian cancers. The specification suggests that immunotherapy directed at the CAK1 antigen (mesothelin/SEQ ID NO:2) should take into account the potential risk of damaging normal mesothelial cells and perhaps cells of the trachea (p. 2, lines 27-37). The antigen has been characterized using the ovarian cancer cell line OVCAR-3 as well as HeLa cells and is a 40 kD glycoprotein attached to the cell surface by phosphatidylinositol. When attempting to clone a cDNA encoding mesothelin, two cloned cDNAs encoding two different intracellular proteins which also react with MabK1 were isolated and neither of these is the cell surface membrane antigen of the claimed invention (p. 3, lines 1-12). The 40kD glycoprotein is processed from a preprotein of 69 kD (p. 3, lines 22-24). The specification hypothesizes that antibodies to mesothelin would be useful in inhibiting the spread or implantation of ovarian cancer cells to the peritoneal wall and without intending to be bound by theory, the instant inventors believe that the antigen is likely responsible for the adhesion and implantation of ovarian carcinoma cells since mesothelin transfectants are more slowly removed from culture dishes than non-transfected cells (p. 10, lines 20-32). Mesothelin is very abundant in normal mesothelial cells from which malignant mesotheliomas and ovarian cystadenocarcinomas are derived and the specification hypothesizes that mesothelin likely has a role in the aggressive spread of these tumors throughout the peritoneal or thoracic cavity (p. 11, lines 4-9). The specification suggests that the detection of mesothelin is useful as an indicator of the presence of tumor cells (p.

11, lines 17-18) and states that the administration of peptides is well known for a variety of diseases and that one of skill is able to extrapolate the information available for use of peptides to treat diseases associated with mesothelin with mesothelin peptides or antibodies to mesothelin (para bridging pages 37-38). The specification further teaches vaccines comprising SEQ ID NO:2 or fragments thereof for the prevention of and inhibition of the growth of tumors bearing mesothelin (p. 44, lines 10-15). The specification teaches that polynucleotide encoding mesothelin, SEQ ID NO:2 was isolated from HeLa cells (p. 49, para 2) and that Northern blot analysis of OVCAR-3, KB, MCF-7 (a breast cancer cell line), A431 (a squamous cell carcinoma cell line) and WI38 (lung fibroblast cell line) demonstrated that mRNA was expressed in OVCAR-2 cells and KB (a HeLa subclone) cells but not in the other cell lines tested (p. 50, para 4). The cloned cDNA encoding SEQ ID NO:2 was transfected into and expressed in mammalian cells (p. 51). The specification states that SEQ ID NO:1 is found on mesothelium, mesotheliomas, ovarian cancers and some squamous cell carcinomas (p. 55, Section C). Finally the specification states that the amino terminal fragment has recently been detected in the medium of OVCAR-3 cells (p. 56).

One cannot extrapolate the teaching of the specification to the enablement of the claims because although the specification teaches that SEQ ID NO:2 would be a useful target for detection and therapy of ovarian cancers and mesotheliomas, and that antibodies to SEQ ID NO:2 would be useful in the inhibition of the spread and implanatation of ovarian cancer cells, the specification also teaches that SEQ ID NO:2 is very abundant in normal mesothelial cells from which malignant mesotheliomas and ovarian cystadenocarcinomas are derived. The specification does not teach that SEQ ID NO:2 is differentially expressed in normal mesothelial

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cells compared with malignant mesotheliomas and ovarian cystadenocarcinomas. In view of the teachings of the specification, it must be assumed that there is no differential expression since the specification specifically teaches that SEQ ID NO:2 is abundantly expressed in normal tissue. If indeed there is no differential between the malignant tissue expression and the normal expression, it is not clear how the expression of SEQ ID NO:2 could be used to detect cancer and it is certainly unclear as to how to use SEQ ID NO:2 to treat cancer, given that the specification specifically teaches that the use of the antigen in treatment would be expected to damage normal mesothelial cells as well as cells of the trachea. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

5. If Applicant were able to overcome the rejection under 35 USC 112, first paragraph above, Claims 19-25, 27-32 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein comprising SEQ ID NO:2, does not reasonably provide enablement for an isolated protein comprising a (emphasis added) full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, a composition comprising a peptide comprising at least 10 contiguous amino acids of mesothelin.

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The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides. This means isolated proteins having up to 10% different amino acid sequence than that of SEQ ID NO:2, isolated polypeptides comprising fragments of SEQ ID NO:2,

The specification teaches that it would be useful to have antibodies that recognize differentiation antigens on solid tumors but that only a small number of these are available (p. 1, lines 34-40) and further teaches that an antibody previously isolated reacts with many ovarian cancers and mesotheliomas as well as normal mesothelial cells as well as some cells in the trachea (p. 2, lines 20-25). The antigen recognized by MabK1 appears to be a differentiation antigen present on mesothelium and is expressed on cancers derived from mesothelium as well as on most ovarian cancers. The specification suggests that immunotherapy directed at the CAK1 antigen (mesothelin/SEQ ID NO:2) should take into account the potential risk of damaging normal mesothelial cells and perhaps cells of the trachea (p. 2, lines 27-37). The antigen has been characterized using the ovarian cancer cell line OVCAR-3 as well as HeLa cells and is a 40 kD glycoprotein attached to the cell surface by phosphatidylinositol. When attempting to clone a cDNA encoding the mesothelin, two cloned cDNAs encoding two different intracellular proteins

which also react with Mab K1 were isolated and neither of these is the cell surface membrane antigen of the claimed invention (p. 3, lines 1-12). The 40kD glycoprotein is processed from a preprotein of 69 kD (p. 3, lines 22-24). The specification hypothesizes that antibodies to mesothelin would be useful in inhibiting the spread or implantation of ovarian cancer cells knot the peritoneal wall and without intending to be bound by theory, the instant inventors believe that the antigen is likely responsible for the adhesion and implantation of ovarian carcinoma cells since mesothelin transfectants are more slowly removed from culture dishes than non-transfected cells (p. 10, lines 20-32). Mesothelin is very abundant in normal mesothelial cells from which malignant mesotheliomas and ovarian cystadenocarcinomas are derived and the specification hypothesizes that mesothelin likely has a role in the aggressive spread of these tumors throughout the peritoneal or thoracic cavity (p. 11, lines 4-9). The specification suggests that the detection of mesothelin is useful as an indicator of the presence of tumor cells (p. 11, lines 17-18) and states that the administration of peptides is well known for a variety of diseases and that one of skill is able to extrapolate the information available for use of peptides to treat diseases associated with mesothelin with mesothelin peptides or antibodies to mesothelin (para bridging pages 37-38). The specification further teaches vaccines comprising SEQ ID NO:2 or fragments thereof for the prevention of and inhibition of the growth of tumors bearing mesothelin (p. 44, lines 10-15). The specification teaches that polynucleotide encoding mesothelin, SEQ ID NO:2 was isolated from HeLa cells (a HeLa subclone) (p. 49, para 2) and that Northern blot analysis of OVCAR-3, KB, MCF-7 (a breast cancer cell line), A431 (a squamous cell carcinoma cell line) and WI38 (lung fibroblast cell line) demonstrated that mRNA was expressed in OVCAR-2

cells and KB cells but not in the other cell lines tested (p. 50, para 4). The cloned cDNA encoding SEQ ID NO:2 was transfected into and expressed in mammalian cells (p. 51). The specification states that SEQ ID NO:1 is found on mesothelium, mesotheliomas, ovarian cancers and some squamous cell carcinomas (p. 55, Section C). Finally the specification states that the amino terminal fragment has recently been detected in the medium of OVCAR-3 cells (p. 56).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification provides no guidance on whether any variant, as claimed, is expressed on any cell and given the novelty of the claimed invention it cannot be predicted, based on the information in the specification or the art of record whether or not such a variant in fact exists. Given the novel nature of the instant invention, it is noted that MPEP 2164.03 teaches that “the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling.” The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill

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in the art to predict that the claimed invention even exists with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Further, even if a function of SEQ ID NO:2 were known at the time the invention was made, it is well known in the art that the art of protein chemistry is highly unpredictable. In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with

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alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen.

These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with a 10% dissimilarity the function of the claimed variants could not be predicted, even if a function were known, based on sequence similarity with SEQ ID NO:2, nor would it be expected to be the same as that of SEQ ID NO:2.

Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the

reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al, Scott et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 10% dissimilarity to SEQ ID NO:2, the function of the claimed variants, even if that of SEQ ID NO:2 were known,

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could not be predicted, based on sequence similarity with SEQ ID NO:2, nor would it be expected to be the same as that of SEQ ID NO:2. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

As drawn specifically to the claimed isolated variant peptides used as immunogens, as suggested by the specification, for raising antibodies that recognize full-length SEQ ID NO:2, even if the peptides claimed were 100% identical to portions of SEQ ID NO:2 it would not be possible to determine with any predictability whether the antibodies produced from a fragment that is specific for SEQ ID NO:2 actually bind to SEQ ID NO: 2, as it cannot be predicted, given the information in the specification, which of the sequences are exposed on the surface of SEQ ID NO:2. Roitt et al, 1998, Immunology, 4th ed, Mosby, London teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). This is exemplified by the teaching of Holmes (Exp. Opin.Invest. Drugs, 2001, 10(3):511-519) who teaches that rabbits were immunized with synthetic peptides which in each case generated high anti-peptide specific immunoreactivities, however, none of the

antibodies exhibited binding to the full length antigen. The author concludes that 'Presumably, expression of these epitopes in the context of the protein was important and affected the antibody binding ability (p. 513, col 1). Furthermore, the specification does not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quaternary structure of a protein in a physiological situation. Further, there is no teaching in the specification of which part of the protein should be used to produce antibodies which will bind specifically to SEQ ID NO:2.

Moreover, as written, the claims encompass defined specific epitopes of SEQ ID NO:2. However, there is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes of the claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999)). Even when the epitope is defined, in terms of the spatial organization of residues making contact with

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ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). Since the specification has not identified which amino acids and or polypeptide fragments are critical or essential characteristics of the epitope, it would not be predictable that the claimed peptides would in fact be specific epitopes of SEQ ID NO:2 or that antibodies produced against these peptides would in fact bind to SEQ ID NO:2. Given the above, given the teachings of Bowie et al that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and teachings of Burgess et al, Lazar et al, Scott et al drawn to the effects of the alteration of even a single amino acid, even if specific peptides of the invention were found to produce antibodies that bind to SEQ ID NO:2, it could not be predicted that the claimed variants would also function to produce antibodies that would bind to SEQ ID NO:2.

As drawn to the recognition of the claimed variant peptides by T-cells from patients with mesothelioma-or ovarian cancer-cells expressing mesothelin, even if the peptides claimed were 100% identical to portions of SEQ ID NO:2 it would not be possible to determine with any predictability which of the peptides of SEQ ID NO:2 comprise T cell epitopes that would be recognized by T-cells from cancer patients. In particular, Kirkin et al, 1998, APMIS, 106 : 665-679 et al teach that in particular for tumor antigens, for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Further, Chaux et al, Int J Cancer, 1998, 77: 538-542 teach some of the CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which is different from the *in vitro* conditions in which the synthetic

peptides are in high number when incubated with the cells (p.541, second column, second paragraph). Given the above, even if a peptide was recognized by T-cells *in vitro* from patients with mesothelioma or ovarian cancer cells expressing mesothelin, it could not be predicted that the T-cells would recognize these peptides *in vivo* and if not recognized *in vivo*, it is clear that one would not know how to use the claimed peptides. Similarly Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54 teach that self-tolerance may eliminate T cells that are capable of recognizing T-cell epitopes with high avidity. Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limit the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484). Given the above, one would not know how to make or use the claimed peptides which could be recognized by T-cells from cancer patients.

Further, it appears that although Applicant has amended the claims to delete reference to a vaccine for the inhibition of mesotheliomas or ovarian tumors, the claims as they are drawn to peptides with T-cell epitopes still read on a vaccine since the only contemplated use for peptides as drawn to T-cell's is for vaccination for the inhibition of mesothelioma or ovarian tumors. Thus, essentially for the reasons previously set forth in the Paper mailed December 19, 2001, Section 6, pages 3-5, claims 20-32 are rejected under 35 USC 112, first paragraph. Further, as drawn to cancer vaccines, Boon (Adv Can Res, 1992, 58:177-210) teaches that for

active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence, as set forth above, suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Thus based on the teaching in the art and in the specification, one cannot predict that an adequate *in vivo* T cell response useful for immunotherapy, as contemplated, could be induced by the peptides of the invention in having tumor burden. In addition, as drawn to peptide tumor vaccines for the induction of a T-cell response, Kirkin et al, Supra review several melanoma-associated antigens, including NY-ESO1, and conclude that initiation of a strong immune response *in vivo* is an extremely rare event (p.674, first column, last paragraph). Kirkin et al teach that for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Kirkin et al teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL *in vitro*, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response *in vivo*, only one of the peptides, peptide EVDPIGHL Y of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Further, even this peptide EVDPIGHL Y of MAGE-A3 produces a very low level of CTL response which is detectable only by a very sensitive method, as taught by Chaux et al, Int J Cancer, 1998, 77: 538-

542, abstract. Given the above, given the teachings of Bowie et al that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and teachings of Burgess et al, Lazar et al, Scott et al drawn to the effects of the alteration of even a single amino acid, even if specific peptides of the invention were found to adequately stimulate T-cell response wherein T cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin recognize said peptides and function as contemplated, it could not be predicted that the claimed variants would also function to adequately stimulate T-cell response wherein T cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin would recognize said peptide and function as contemplated. Given the unpredictability that any fragment or any portion of SEQ ID NO:2 would elicit an adequate T cell response *in vivo*, useful for the inhibition of cancer, as contemplated, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Applicant's arguments drawn to the rejection of claim 17 in the Paper mailed December 19, 2001 are relevant to the instant rejection drawn to the issue of T-cell recognition and vaccine.

Applicant argues that there is no requirement for a vaccine to cure a disease to be useful or enabled. The argument has been considered but is not found persuasive for the reasons set forth above drawn to the unpredictability of peptide vaccines.

Applicant argues that the claims are enabled as they are drawn to compositions to be administered to animals to raise antibodies to mesothelin. The argument has been considered but has not been found persuasive for the reasons set forth above, and further, the instant rejection is drawn specifically to the T-cell embodiments claimed.

Applicant argues that (a) the claims are not drawn to the replacement of standard therapies, (b) the Spitler reference is based on whole cell vaccines of the late 1980's and early 1990's, (c) Evans et al state that the notion that the immune system can be activated by cancer vaccines to attack and reject established tumors is a fact. The arguments have been considered but have not been found persuasive because (a')(b')(c') the references set forth previously and above clearly delineate the unpredictability to the art as it is drawn to peptide vaccines.

6. Claims 20-26, 30-32 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "at least 90% sequence identity" a has no clear support in the specification and the claims as originally filed. Applicant argues that support can be found for the newly added limitation, in particular, at page 15, lines 1-14, page 46, lines 24-37 and page 6, lines 19-30. A review of the specification discloses support for recombinant or synthetic polypeptides of 10 amino acids in length or greater which can be used as immunogens for the production of antibodies at page 15, lines one through 14. A review of the specification discloses support for the necessity to expose a mammal to appropriate epitopes in order to elicit effective immuno protection and the routine alteration of natural proteins primary structure to create derivatives embracing epitopes that are identical to or substantially the same as naturally occurring epitopes at page 46, lines 24-37. A review of the

specification discloses support for the definition of substantial similarity wherein substantial similarity, in the context of a polypeptide, is 90% identity over a comparison window of about 10-20 amino acid residues at page six lines 19-30. It is noted that the claims do not recite the limitation of 90% identity over a comparison window of about 10-20 amino acids. In the absence of that limitation the subject matter claimed in claims 20-26, 30-32 broadens the scope of the invention as originally disclosed in the specification.

7. Claims 22 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "10 or more contiguous peptides" has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for peptides comprising 10 or more contiguous amino acids, but not to 10 or more contiguous peptides of SEQ ID No:2. The subject matter claimed in claim 22 broadens the scope of the invention as originally disclosed in the specification.

8. Claims 19-25, 27-32 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 19-25, 27-32 are drawn to an isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo

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Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that [a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials. *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Id.*

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristicsi.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Thus, the instant specification may provide an adequate written description of an isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin, per Lilly by structurally describing a representative number of isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide

comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin or by describing □ structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete □ by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ

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ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin other than SEQ ID NO:2, nor does the specification provide any partial structure of such isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin, nor any physical or chemical characteristics of the isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin nor any

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functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID NO:2, this does not provide a description of isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin that would satisfy the standard set out in Enzo.

The specification also fails to describe the isolated protein comprising SEQ ID NO:2, an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin by the test set out in Lilly. The specification describes only SEQ ID NO:2 and thus necessarily fails to describe a representative number of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of the an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides wherein when used as an immunogen, raises antibodies which recognize full-length mesothelin or is recognized by T-cells from patients with mesothelioma or ovarian cancer cells expressing mesothelin that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed synthetic cross-linker protein is capable of binding, it also fails to adequately describe the synthetic cross-linker protein.

9. Claim 19 is rejected under 35 USC 112, second paragraph because it recites a "a full-length amino acid sequence of SEQ ID No: 2". The claim is confusing because it cannot be determined whether a full-length amino acid sequence of SEQ ID NO:2 refers to the full-length of SEQ ID No:2 or to full-length fragments within SEQ ID No:2.

10. Claim 32 is rejected under 35 USC 112, second paragraph because there is no antecedent basis for the phrase "mesothelin-derived peptide" in claim 30 from which it depends.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 19-25, 27-32 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chang et al, Cancer Research, 1992, 52:181-186.

It is not possible to determine from the information available in the imaged specification and sequence listing whether the “full length” 69 kDa protein is SEQ ID NO:2 or whether SEQ ID NO:2 is the processed 40 kDa protein, thus it will be assumed for examination purposes that SEQ ID NO:2 is the amino acid sequence of the 69 kDa protein. Should, however, it be determined that SEQ ID NO:2 is the 40 kDa protein, then claim 26 will also be included in the instant rejection.

It is noted that for examination purposes, due to the indefinite language of claim 19 that the limitation, “an isolated protein comprising a (emphasis added) full-length amino acid sequence of SEQ ID NO:2”, is understood to mean an isolated protein comprising a full length fragment of any size of SEQ ID NO:2. Further, since the sequence of the 40 kDa fragment is unknown, it will be assumed for examination purposes that the 40 kDa fragment comprises at least 90% of SEQ ID NO:2.

The claims are drawn to an isolated protein comprising a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2, compositions comprising said proteins and peptides, wherein SEQ ID NO:2 is named CAK1, is found in human mesothelia and nonmucinous ovarian tumors and was isolated and characterized by Kai Chang et al.

Chang et al specifically teaches an isolated 40 kDa CAK1 protein (see Fig. 3, p. 184, and Discussion, col 2, p. 184) which clearly comprises a full-length amino acid sequence of SEQ ID NO:2, an isolated protein having at least 90% identity to SEQ ID NO:2, an isolated peptide comprising at least 10 amino acids, which peptide has at least 90% identity to a sequence of at least 10 contiguous amino acids of SEQ ID NO:2, which comprises 10 or more contiguous peptides of SEQ ID NO:2. Although the reference does not recite SEQ ID NO:2, given that the protein is isolated from the same source, binds to the same antibody, it appears that the prior art protein and the claimed protein are the same, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

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13. All other objections and rejections recited in the paper mailed December 19, 2001 are hereby withdrawn.

14. Amendment of the claims necessitated the new rejections, thus, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 872-9306.

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Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

A handwritten signature in cursive script, appearing to read "Susan Ungar".

Susan Ungar
Primary Patent Examiner
August 4, 2004